IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	Confirmation No.: 6830
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Jane HIRSH	)	Group Art Unit: 1618
	)	
Application Number: 10/690,872	)	Examiner: Leah H. Schlientz
	)	
Filed: October 22, 2003	)	
	)	
For: PULSATILE RELEASE COMPOSITIONS OF MILNACIPRAN		

DECLARATION OF ALISON B. FLEMING UNDER 37 C.F.R. § 1.132

I, Alison B. Fleming, do hereby declare that:

1. I am a citizen of the United States residing at 126 Union Street, Mansfield, MA 02048.

2. I am Senior Director of Product Research and Development at Collegium Pharmaceutical, Inc. My duties include, among others, the management and direct supervision of novel oral formulation development projects for active compounds and the review and analysis of *in vitro* dissolution data and *in vivo* pharmacokinetic data..

3. I received my Ph.D. from Cornell University in 2003 in the field of Chemical Engineering with a minor in Pharmacology. My Ph.D. research focused on implantable, controlled-release drug delivery systems. I received my BS from University of Massachusetts Amherst in 1997, where I majored in Chemical Engineering, with a minor in Chemistry.

4. I have reviewed the claims that are currently before the examiner in the captioned application. I understand that the invention is currently claimed as follows:

   A milnacipran formulation that provides pulsatile release of milnacipran wherein the formulation comprises:

(a) an immediate release solid dosage unit comprising a first dose of milnacipran that is released substantially immediately following oral administration of the formulation to a patient, resulting in a first plasma level peak at a time between approximately 0.05 hours to less than approximately 3 hours following oral administration; and
(b) a delayed release solid dosage unit comprising a delayed release polymer and a second dose of milnacipran that is released 3 to 10 hours following oral administration of the formulation;
wherein there is a lag time where there is substantially no release of milnacipran between the release of milnacipran from the immediate release solid dosage unit and the release of milnacipran from the delayed release solid dosage unit; and
wherein the formulation produces a therapeutic effect over 24 hours when administered to a patient in need thereof with diminished incidence or reduced intensity relative to side effects resulting from administration of the same dose of milnacipran administered in an immediate release formulation.

5. The above claim recites two separate releases of milnacipran, the first occurring immediately and the second occurring 3 to 10 hours following oral administration of the formulation. The claim also provides that following the first release, there results "a first plasma level peak at a time between approximately 0.05 hours to less than approximately 3 hours." This language reflects the fact that although the drug is released substantially immediately upon ingestion, absorption of the drug (ie, transfer from the GI tract into the circulatory system) occurs over a period of time following release. Although not explicitly recited, there is likewise an absorption timeframe following the second release at 3 to 10 hours, wherein the drug is present in the GI tract and available for absorption, which occurs for a period of five or more hours.[1]

[1] The absorption period following the first release of milnacipran is shorter than the absorption period corresponding to the second release of milnacipran. Two factors may
(continued...)

Indeed, for reasons discussed in detail below, even where the second release of the drug occurs early in the claimed range, *i.e.*, near three hours, there will still be absorption of a therapeutically significant amount of the drug for a period corresponding to a time when the drug is in the colonic region of a patient, corresponding to five or more hours. Accordingly, in reciting a 3 to 10 hour release of the second dose, the claim necessarily requires that a significant amount of the milnacipran be absorbed colonically.

6. As shown in Figure 2 on page 36 of the Keller declaration filed on January 3, 2008 (attached hereto as Exhibit C), the delayed release solid dosage unit begins to release milnacipran such that one observes an increase in the plasma concentration of milnacipran after about 3 hours following the oral administration of the claimed pulsatile formulation. The absorption of milnacipran **must** continue for about another four hours because, as seen in Figure 2 of the Keller declaration, the plasma concentration of milnacipran continues to rise until it peaks after about 8 or 9 hours following the administration of the claimed pulsatile formulation. The claimed pulsatile formulation, therefore, delivers milnacipran for the entire period of 3 to 8 or 9 hours following oral administration of the formulation. This time period is encompassed by the claimed period of 3 to 10 hours following oral administration of the formulation. And, during that period, milnacipran is being absorbed.

7. At the time the invention was made, one of ordinary skill in the art had a reasonable expectation that after about five hours from ingestion in the fasted state a drug dosage form would be exiting the ileocolonic junction (ICJ) and entering the colon. Ian R. Wilding and David V. Prior, *Therapeutic Drug Carrier Sys. 20*: 405-431 (2003). After about 8 or 9 hours from ingestion of a drug dosage form, under fed or fasted

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contribute to the observed difference: (1) disintegration of the dosage form may be faster in the stomach than in lower regions of the GI tract where less water is available to dissolve the formulation; and (2) absorption of the drug will likely be faster in the upper regions of the GI tract than in the lower small intestine and colon due to the relative rates of drug permeation in these regions. (Fagerholm, *Journal of Pharmacy and Pharmacology 59*:905-916 (2007)).

conditions, one would expect the formulation to be in the colon. *Id.* In sum, the claimed pulsatile formulation must deliver a substantial amount of milnacipran to the colon, where the milnacipran is readily absorbed with high efficiency. As discussed in further detail below, this result is contrary to what one with ordinary skill would have expected to observe for a drug as lipophobic as milnacipran.

8. I have reviewed and analyzed the Office Action dated November 13, 2008 ("the Office Action") that issued in connection with the captioned application. In the Office Action, claims 1-3, 6-10, 15-17, 19-21, and 25-28 have been held obvious over the disclosure of U.S. Patent No. 6,340,476 to Midha *et al.* in combination with Marc Ansseau *et al.*, 114 *Psychopharmacology* 131-137 (1994). In the Office Action, claims 1-3, 6-12, 15-17, and 19-21 have been held obvious over the disclosure of Midha in combination with Ansseau and U.S. Patent No. 6,699,506 to Paillard *et al.* In the Office Action, claims 1-3, 6-12, 14-17, and 19-21 have been held obvious over the disclosure of Midha in combination with Ansseau and Published U.S. Appl. No. 2003/0203055 to Rao *et al.* In the Office Action, claims 1-3, 6-10, 15-17, 19-21, and 25-28 have been held obvious over the disclosure of Midha in combination with Ansseau, Neliat *et al.*, 35 *Neuropharmacology* 589, 592 (1996), and U.S. Patent No. 6,228,398 to Devane *et al.* In the Office Action, claims 1-3, 6-10, 15-17, 19-21, and 25-28 have been held obvious over the disclosure of Midha in combination with Ansseau, Neliat, and U.S. Patent No. 7,008,640 to Watanabe *et al.*

9. I understand that an invention is considered to be obvious under the law if the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art, such as myself, at the time the invention was made. I further understand that when modifying a reference or combining the teachings of two or more references, one of ordinary skill in the art (1) must have had some reason, for example a teaching suggestion or motivation, to modify or combine the reference and (2) must have had a reasonable expectation of success that the modification or combination would work

10. In this Declaration I will primarily address the fact that the pending claims are not *prima facie* obvious over the disclosure of Midha (the primary reference on which all of the rejections in the Office Action rely). The key reasons why the pending claims are not *prima facie* obvious is because (1) one of ordinary skill in the art would have had no reason to employ a drug such as milnacipran in a pulsatile release system as claimed and (2) even if there had been some reason to employ milnacipran in a pulsatile release system, one of ordinary skill in the art would not have had a reasonable expectation of success that a highly lipophobic drug such as milnacipran could be fully absorbed by the human body when released according to the profile claimed for the delayed release solid dosage unit, *i.e.*, 3 to 10 hours following oral administration of the formulation, since such a release profile would rely on absorption, at least partially, in the colon.

11. It is well known that lipo**philic** drugs would be expected to be absorbed well in the colon. It is also well known that lipo**phobic** drugs (*e.g.*, polar drugs) would not be expected to be absorbed well in the colon. *See*, *e.g.*, S. A. Riley *et al.*, *Aliment. Pharmacol. Ther. 6*: 701-706 (1992) (Exhibit A); P. Artursson, *J. Pharm. Sci. 79*: 476-482 (1990) (Exhibit B); and U. Fagerholm, *J. Pharmacy and Pharmacology 59*: 905-916 (2007) (Exhibit C). Midha, the primary reference on which all of the present rejections rely, teaches formulations that release methylphenidate, a lipophilic drug, in a pulsatile fashion. Devane, like Midha, teaches formulations that release methylphenidate in a pulsatile fashion.

12. It would appear, from my review of the art cited in the Office Action, that drugs that are well-suited for formulation into a pulsatile release system are those that have a half-life that is less than about three hours and are expected to be absorbed in the lower regions of the GI tract, including the colon. In contrast, at the time the claimed invention was made, one of ordinary skill in the art would *not* have predicted that a hydrophilic/lipophobic drug such as milnacipran would be effectively colonically absorbed and thus would not have attempted to deliver milnacipran in a pulsed fashion. Midha and Devane disclose that methylphenidate is a drug that is well-suited

for formulation into a pulsatile release system for a number of reasons,[2] including the fact that methylphenidate has a short half life. The half life of methylphenidate is 2.1 hours in adults. *See* http://www.mentalhealth.com/drug/p30-r03.html (last visited May 12, 2009). Other drugs that are discussed in the art cited in the Office Action include ketoprofen and ibuprofen. *See* Devane 2:39-3:2. Ketoprofen has a half life of 1-3 hours. *See* Devane 2:41-45. Ibuprofen has a half life of 1.8-2 hours. *See* http://www.healthcareprescriptiondrugabuse.com/Ibuprofen.html (last visited May 12, 2009). It is my belief that methylphenidate, ketoprofen, and ibuprofen, are lipophilic drugs. *See, e.g.*, http://uuhsc.utah.edu/pharmacy/bulletins/NDB_112.pdf (for methylphenidate); T. Ngawhirunpat *et al.*, *Pharmazie 56*: 231-234 (2001) (for ketoprofen); F.R. Formiga *et al.*, *Int'l J. of Pharmaceutics 344*: 158-160 (2007) (for ibuprofen). In contrast to methylphenidate, ketoprofen, and ibuprofen, milnacipran is highly lipophobic and has a half life that is significantly longer than the half life of the compounds disclosed in the art cited in the Office Action. For example, at seven hours,[3] the half life of milnacipran is over three times longer than that of methylphenidate and over two to seven times longer than the half life for ketoprofen. Accordingly, it is my opinion, at least because milnacipran has a relatively long half life and is lipophobic in nature, that one of ordinary skill in the art would have had no reason to employ a drug such as milnacipran in a pulsatile release system as claimed.

13. It is also my opinion that the prior art does not render the claimed formulation obvious even if there would have been a reason to formulate milnacipran into a pulsatile release system. As set forth above, the recitation in the claim of release at three to ten hours following administration means that the drug is absorbed during the period in which it is in the colonic region. However, at the time of the present invention, one of ordinary skill in the art would not have had a reasonable expectation

[2] Other reasons include the fact that methylphenidate has a potential for tolerance (loss of clinical efficacy when constant blood levels are maintained) and potential for abuse. *See* Midha 2:39-43. To my knowledge, milnacipran does not share these features with methylphenidate.

[3] http://www.answers.com/topic/milnacipran (last visited May 12, 2009).

of success of obtaining a pulsatile formulation of a drug having the chemical and pharmacokinetic properties of milnacipran that a) provides a release spectrum where the milnacipran is released 3 to 10 hours following oral administration of the formulation; b) provides an absorption spectrum where a substantial amount of the milnacipran that is released is very efficiently absorbed in the colon; and c) provides a release profile that results in therapeutically effective plasma levels over approximately 24 hours.

14. One of ordinary skill in the art would have had a reasonable expectation that a lipophilic drug, such as Midha's methylphenidate, would be colonically absorbed. Accordingly, the skilled artisan would have been motivated to produce the pulsatile drug dosage form taught by Midha to deliver a lipophilic drug that is absorbed as far down the gastrointestinal tract as the colon. But the person of skill in the art would not have had a reasonable expectation that a drug such as milnacipran, which is highly lipophobic, would be colonically absorbed and certainly not as well as the inventors observed.

15. At the time the claimed invention was made, one of ordinary skill in the art would *not* have predicted that a hydrophilic/lipophobic drug such as milnacipran would be effectively colonically absorbed. Instead, the skilled artisan would have wanted to release a drug as hydrophilic/lipophobic as milnacipran relatively quickly because it is well known that lipophobic drugs like milnacipran are absorbed best in areas of the higher gastrointestinal tract (*e.g.*, not as far down the GI tract as the colon).

16. In sum, therefore, the prior art, including Midha and Devane, does not provide a reasonable expectation of success that a highly lipophobic drug such as milnacipran could be fully absorbed by the human body when colonic absorption is required according to the profile claimed for the delayed release solid dosage unit, *i.e.*, 3 to 10 hours following oral administration of the formulation.

17. I declare further that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further, these statements were made with the knowledge, that willful false statement and the like thereof made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and such willful false statements may jeopardize the validity of the above-named application or any patent issuing thereon.

Respectfully submitted,

Date: 05/13/09

By: 
Alison B. Fleming